Cerebral perfusion SPET correlated with Braak pathological stage in Alzheimer’s disease


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Summary
Reductions in regional cerebral perfusion, particularly in the posterior temporo-parietal lobes, are well recognized in Alzheimer’s disease. We set out to correlate perfusion changes, using 99mTc-HMPAO single photon emission tomography (SPET), with the pathological stage of Alzheimer’s disease. The ‘Braak stage’ of the distribution of neurofibrillary pathology in post-mortem brains was used to classify SPET scans taken in life from a mixed (dementia and control) elderly population into the entorhinal stage (n = 23 subjects), limbic stage (n = 30 subjects) and neocortical stage (n = 36 subjects) Alzheimer’s disease pathology. The SPET scans were then registered to a common, standard Talaraich space, and single template scans produced for each pathological stage. Comparison of these templates revealed an evolution in the pattern of reduction in regional perfusion. Additional comparisons were performed using earlier SPET scans obtained 5 years before death. For comparisons between templates, a threshold of 10% perfusion change was chosen so as to be clinically relevant as well as statistically significant. Reduced perfusion appears between the entorhinal and limbic stages in the anterior medial temporal lobe, subcallosal area, posterior cingulate cortex, precuneus and possibly the supero-anterior aspects of the cerebellar hemispheres. Large posterior temporo-parietal perfusion defects then appear between the limbic and neocortical stages, before finally large frontal lobe perfusion defects. The time course of these perfusion defects appears relatively long, suggesting that perfusion changes may have scope to be a diagnostic aid in staging Alzheimer’s disease in life. The reduction in anterior medial temporal lobe perfusion may have future relevance on modern high resolution SPET and PET systems and also perfusion-type MRI sequences.

Keywords: Alzheimer’s disease; brain; physiopathology; Braak stage; radionuclide imaging; SPET

Abbreviations: OPTIMA = Oxford Project to Investigate Memory and Ageing; SPET = single photon emission computed tomography; 99mTc-HMPAO = technetium 99m–hexamethylpropyleneamineoxime

Introduction
Diagnostic aids are required in dementia and memory impairment. Clinical diagnosis of the cause of early memory problems is notoriously poor. Even in dementia, if strict clinical criteria are used, such as the NINCDS (National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association) criteria (McKhann et al., 1984) for probable Alzheimer’s disease, then, although specificity is improved, sensitivity suffers. This may help interpretation of published research studies, but is of little day-to-day clinical value. When the first 118 consecutive post-mortem OPTIMA (Oxford Project to Investigate Memory and Ageing) cases were compared with CERAD (Consortium to Establish a Registry for Alzheimer’s disease) (Mirra et al., 1991) histological criteria, NINCDS possible Alzheimer’s disease was 93% sensitive, 61% specific, and NINCDS probable Alzheimer’s disease was only 49% sensitive and 100% specific (Jobst et al., 1998). Research studies often have the benefit of observing the evolution of a subject’s dementia, a vital clinical tool, but a luxury not afforded to a busy clinician referring new patients to a memory clinic. Furthermore, it is likely that specific disease-modifying drugs will become available for Alzheimer’s disease which will slow, or hopefully arrest, the pathological processes. To be of maximum benefit, these drugs would need to be administered early in the course of the disease before
irreversible loss of vital neurones. This will increase the pressure for early, accurate diagnosis at the time of greatest clinical uncertainty.

Functional brain imaging has a long history in dementia. Of the many hundreds of publications, very few have used the gold standard of histology. Not only does this lead to doubts over clinical diagnosis but also, in comparison studies with ‘healthy aged’, there is a significant chance that some members of the control group are contaminated by clinically occult Alzheimer’s disease pathology. Nevertheless, there is overwhelming evidence that Alzheimer’s disease is associated with a decrease in metabolism and perfusion of the posterior temporo-parietal region in the resting state. This was shown initially by a $^{133}$Xe regional cerebral blood flow technique using small surface scintillation detectors (Ingvar et al., 1975) and then with $^{15}$O PET (Frackowiak et al., 1981) and $^{[18F]}$deoxyglucose PET (Benson et al., 1983; Friedland et al., 1983) before single photon emission computed tomography (SPET) with $^{[123I]}$iofetamine (Jagust et al., 1987; Johnson et al., 1987) and numerous studies with the perfusion marker technetium 99m–hexamethylpropylene-amineoxime ($^{99mTc}$-HMPAO) (Burns et al., 1989; Holman et al., 1992; Jagust et al., 2001). No other region has been demonstrated consistently to have abnormal metabolism or perfusion. This may be due to the wide spectrum of disease stages, in clinical series, often with modest subject numbers. Furthermore, if reliable clinical identification of prodromal or early cases of Alzheimer’s disease were possible, there would be no need to search for brain imaging diagnostic aids. Hence, correlation is required with both pathologically confirmed diagnoses and stage of disease.

It has been proposed that there is a progression of neurofibrillary pathology from the transentorhinal and entorhinal cortex to the hippocampus, and then to the remaining limbic system before involving other cortical regions, followed by the primary motor and somatosensory cortices, and finally the occipital cortex (Braak and Braak, 1999). This progression is the basis of the Braak staging. There is evidence that declines in memory test performance and then mental state tests are associated with the limbic stages, and increasing dementia with progression through the neocortical Braak stages (Delacourte et al., 1999; Grober et al., 1999; Nagy et al., 1999).

The aim of this study was to correlate regional cerebral perfusion demonstrated by $^{99mTc}$-HMPAO SPET with the pathological stage of Alzheimer’s disease based on Braak staging.

**Methods**

**Subjects**

All subjects were volunteers to OPTIMA who completed a cerebral SPET scan between December 1991 and September 1998, and had post-mortem histology. OPTIMA is a prospective, longitudinal, clinicopathological study of ageing, in both ‘control’ elderly and memory-impaired subjects. Informed consent was obtained from those subjects without cognitive deficit and was given by a close relative for those with a significant deficit. Ethical approval was obtained from both the Central Oxford Research and the Psychiatric Sector Research Ethics Committees. Subjects were referred with varying degrees and types of mental deterioration (Jobst et al., 1992b). Controls were volunteers without cognitive dysfunction as assessed by the CAMDEX (Roth et al., 1988).

**SPET acquisition and processing**

All the SPET studies were acquired in an identical manner on the same gamma camera. Subjects were encouraged to relax in a dimly lit room, with music quietly playing in the background and with their eyes closed at the time of the intravenous injection and for several minutes thereafter. $^{99mTc}$-HMPAO (500 MBq; Nycomed Amersham International, Amersham, UK) was administered within 10 min from its constitution.

Images were acquired using a single-head General Electric 400 X/CT gamma camera with an ultra-high resolution collimator. Sixty-four images were obtained over 360°, 20 s per projection, 64 × 64 matrix. Filtered back projection with a Butterworth filter and Sorensen attenuation correction were employed using a Nuclear Diagnostics (Sweden) Hermes workstation and software. The FWHM (full-width half maximum) was 10.5 mm at the centre of rotation; reconstructed slice thickness was 6.44 mm. The reconstructed data were fitted individually onto a standard database template in Talaraich coordinates. This employed a fully automated, linear, nine-parameter (scale, translation and rotation for each of x, y and z) fit initially by a principal axis transformation and subsequently refined by a count difference minimization algorithm (BRASS, Huddinge template, Nuclear Diagnostics, Sweden) (Slomka et al., 1997). A radiologist (K.B.) checked the quality of each fit to the template. In four studies, with prominent paranasal uptake, the fit initially was suboptimal; in these studies, the paranasal uptake was removed by manually drawing a region of interest on the sagittal reconstruction and then excluding it. The automated fitting algorithm was then successful.

Once the studies were in a common, standardized space, they were grouped together according to pathological status. A template was formed for each group using Modelgen software (Nuclear Diagnostics, Sweden). In effect, each template represents the mean SPET scan appearance for that group of subjects and exploits the power of averaging out ‘noise’. Since these templates are registered to the same coordinates in Talairach space, direct comparison is permitted. Hence, any perfusion differences demonstrated do not rely on prior assumptions, since entire brain templates are compared and not just selected regions of interest.
Pathological staging

Brains were fixed in 4% formalin for at least 4 weeks. Blocks were taken from the medial temporal lobe to include the entorhinal cortex and hippocampus and from the occipital lobe (including Brodmann’s areas 17, 18 and 19) and embedded in paraffin. Sections were cut 10 µm thick and stained with the Gallyas impregnation method to visualize Alzheimer’s disease-related neurofibrillary pathology (Gallyas, 1971). Staging was carried out according to the modified recommendations (Braak and Braak, 1991; Nagy et al., 1998). (i) Stages I and II were classified as entorhinal stage Alzheimer’s disease (n = 23 subjects); (ii) stages III and IV as limbic Alzheimer’s disease (n = 30 subjects); and (iii) stages V and VI as neocortical Alzheimer’s disease (n = 36 subjects).

Results

The SPET scans were grouped purely on the basis of Braak stage. Eight scans were excluded due to other pathology and two for technical reasons. The other pathologies were two frontotemporal dementias (both SPETs demonstrating dramatic frontal hypoperfusion), two large infarcts (established in life on CT), one Huntington’s disease, one cortico-basal degeneration, one shunted hydrocephalus, and one man with an unusual pattern of atrophy (on CT) and almost no cerebellar perfusion. The two technical exclusions were for movement artefact and a study with very low counts that could not be fitted to standardized space. No other exclusions were made since our aim was to study subjects with a defined stage of Alzheimer’s disease pathology such as might present at a typical clinic.

Only two subjects (aged 88.3 and 68.6 years) in this study were Braak stage 0, i.e. without any neurofibrillary changes of Alzheimer’s disease type. These scans were compared with the entorhinal template, no significant differences in perfusion were demonstrated. The Braak stage 0 subjects have therefore been omitted and, in effect for this study, baseline becomes the entorhinal stage of Alzheimer’s disease pathology. Table 1 gives the demographics of the subject groups at the time of SPET and their intervals to death.

In the comparisons below, only regions revealing >10% change in counts, relative to a common, absolute scale of counts, are shown. This value was chosen so as to be clinically useful as well as statistically significant, since a region with a 10% reduction in perfusion can usually be reported confidently on an individual’s scan. Similar patterns of changes in perfusion were found for men and women. It was found that all differences were due to reductions in perfusion.

Comparison of last SPETs before death

Entorhinal versus limbic stage

Five regions of hypoperfusion were revealed: (i) anterior medial temporal lobe (Fig. 1a); (ii) subcallosal area [this is a thin band of cortex extending from the anterior cingulate to the genu of the corpus callosum around the medial banks of the frontal lobes (Brodmann areas 25 and 32) inferior to the rostrum of the corpus callosum and narrowing posteriorly to reach the anterior thalamus] (Fig. 1b and d); (iii) posterior cingulate and precuneus (Fig. 1b and c); (iv) tiny rind of the right parietal cortex (Fig. 1b); and (v) superior aspect of both the anterior cerebellar hemispheres (Fig. 1a).

Limbic versus neocortical stage

Large bilateral posterior temporo-parietal defects were seen (Fig. 1e and f). A small ‘cap’ of reduced perfusion was revealed in the left frontal lobe just anterior to the lateral

Table 1 Subject characteristics at time of last SPET

<table>
<thead>
<tr>
<th>Braak stage</th>
<th>n</th>
<th>Last SPET before death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age at SPET (years) mean (SD)</td>
</tr>
<tr>
<td>Entorhinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>76.6 (7.2)</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>80.1 (6.2)</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>78.1 (6.9)</td>
</tr>
<tr>
<td>Limbic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>79.9 (6.3)</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>83.8 (9.4)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>82.0 (8.2)</td>
</tr>
<tr>
<td>Neocortical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>70.7 (7.5)</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>74.5 (6.1)</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>72.8 (6.9)</td>
</tr>
</tbody>
</table>

CAMCOG = Cambridge Cognitive Test; MMSE = Mini-Mental State Examination.
Bilateral anterior frontal perfusion defects became conspicuous at an 8% difference threshold. A reduction in medial temporal lobe perfusion was seen only by reducing the difference threshold to 5%.

**Entorhinal versus neocortical stage**

The regions of relative hypoperfusion were a summation of the entorhinal versus limbic and limbic versus neocortical comparisons. In addition, at the 10% threshold, large
symmetrical regions of mainly anterior frontal lobe hypoperfusion were revealed. When the difference threshold was raised to 15%, differences persisted in the anterior medial temporal lobe, subcallosal region and large posterior temporo-parietal regions.

**Comparison of SPETs taken 5 years before death**
Six subjects in each pathological group (entorhinal, limbic and neocortical) also underwent SPET scanning 5 years (±7 months) before death (Table 2).

Templates were made of both their 5-year pre-death SPETs and their last SPETs pre-death. The 5-year pre-death templates for these subgroups compared as follows.

**Entorhinal versus limbic**
No changes in perfusion were demonstrated at the 10% threshold for this small group. When the difference threshold was reduced to 8%, then a reduction in left anterior medial temporal lobe perfusion was demonstrated.

**Limbic versus neocortical**
Large bilateral temporo-parietal defects were demonstrated.

**Entorhinal versus neocortical**
Large bilateral temporo-parietal defects were demonstrated, almost the same as the previous comparison. Relative frontal hypoperfusion was not demonstrated.

**SPET changes over time**
For a comparison over time, the 5-year pre-death templates of each subgroup were compared with their subsequent last SPET templates. In practice, it was found that if the last SPET templates of the total group (Table 1) were used instead for the comparisons, the results were almost identical.

**Changes for those in the entorhinal stage**
There was a 3.28 year interval. Only a thin line of reduced perfusion outlining the lateral ventricles was revealed, consistent with normal cerebral atrophy (Fig. 1g).

**Changes for those in the limbic stage**
There was a 2.99 year interval. A thin line of reduced perfusion outlining the lateral and third ventricles was revealed. This was greater than in the entorhinal stage group but still consistent with cerebral atrophy.

**Changes for those in the neocortical stage**
There was a 2.44 year interval. Large bilateral regions of anterior frontal reduced perfusion were revealed, plus bilateral temporo-parietal decreases (Fig. 1h).

**Other temporal relationships**
In order to attempt to clarify further the time course of the development of perfusion changes across the stages of Alzheimer’s disease, two additional comparisons were performed. The 5-year pre-death limbic template (n = 6) was compared with the last pre-death entorhinal template (n = 23). This revealed bilateral anterior medial temporal lobe reductions in perfusion (Fig. 1i) matching those demonstrated by

### Table 2 Subjects who also had a SPET scan 5 years before death

<table>
<thead>
<tr>
<th>Braak stage</th>
<th>n</th>
<th>SPET 5 years before death</th>
<th>Last SPET pre-death of subjects with 5-year SPET available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age at SPET (years)</td>
<td>Age at SPET (years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interval from SPET to death (years)</td>
<td>Interval from SPET to death (years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>3</td>
<td>78.2 (7.1)</td>
<td>82.1 (7.3)</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>80.8 (7.2)</td>
<td>83.4 (6.7)</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>80.8 (7.2)</td>
<td>82.8 (6.3)</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>79.5 (6.6)</td>
<td>82.0 (8.1)</td>
</tr>
<tr>
<td>Interval</td>
<td></td>
<td>5.11 (0.23)</td>
<td>4.87 (0.31)</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>79.2 (9.0)</td>
<td>82.9 (7.5)</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>83.4</td>
<td>87.4</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>79.9 (8.2)</td>
<td>82.9 (7.5)</td>
</tr>
<tr>
<td>Limbic</td>
<td></td>
<td>5.02 (0.40)</td>
<td>2.05 (1.71)</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>69.8 (9.8)</td>
<td>72.6 (9.6)</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>74.2</td>
<td>75.1</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>70.6 (9.0)</td>
<td>73.0 (8.7)</td>
</tr>
<tr>
<td>Interval</td>
<td></td>
<td>5.01 (0.44)</td>
<td>5.34</td>
</tr>
<tr>
<td>Neocortical</td>
<td>5</td>
<td>70.6 (9.0)</td>
<td>2.62 (1.19)</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>69.8 (9.8)</td>
<td>73.0 (8.7)</td>
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<tr>
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<td>74.2</td>
<td>75.1</td>
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<tr>
<td>Total</td>
<td>6</td>
<td>70.6 (9.0)</td>
<td>2.62 (1.19)</td>
</tr>
<tr>
<td>Interval</td>
<td></td>
<td>5.06 (0.42)</td>
<td>4.41</td>
</tr>
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</table>
comparing the last SPET limbic template \((n=30)\) with the last SPET entorhinal template. Subcallosal decreases in perfusion were also demonstrated, but smaller in volume and not extending as far posteriorly as in the previous comparison at the same 10% threshold.

Finally, the 5-year pre-death neocortical template \((n=6)\) was compared with the last SPET pre-death limbic template \((n=30)\). This demonstrated a large bilateral posterior temporo-parietal reduction in perfusion. Frontal decreases in perfusion were not found.

The major reductions in perfusion, for comparisons between SPET templates, are summarized in Fig. 2.

**Discussion**

We have been able to show changes in regional cerebral perfusion that are correlated with the progression of Alzheimer’s disease pathology. There is an evolution in regions demonstrating decreases in perfusion. The earliest regions showing perfusion deficits are the anterior medial temporal lobes, subcallosal region and the posterior cingulate region. Then, large posterior temporo-parietal defects develop and, finally, frontal lobe defects sparing the motor and somatosensory cortices.

The earliest perfusion changes and their timing are important if perfusion imaging is to be used as a diagnostic aid in early Alzheimer’s disease. The anterior medial temporal lobe hypoperfusion developing between the entorhinal and limbic stage of Alzheimer’s disease may seem expected since, by definition, this is the site of pathological involvement. Furthermore, it is well established that the medial temporal lobe is a site of early atrophy in Alzheimer’s disease (Jobst et al., 1992b; Jack et al., 1997) and this atrophy would act to exaggerate any perfusion changes in the medial temporal lobe. Perhaps the most surprising aspect of the SPET perfusion and PET metabolism literature in Alzheimer’s disease is the lack of reports concerning the medial temporal lobe. This may be due to technical reasons. Early SPET gamma cameras were typically single headed with, by modern standards, relatively poor scatter and attenuation correction, leading to poor spatial resolution at depth. The medial temporal lobe, therefore, was one of the most difficult regions to image with SPET or PET. Modern multi-headed SPET gamma cameras and PET equipment have a spatial resolution within the deep brain structures, including the medial temporal lobes, which makes observation of the deep brain regions demonstrated in this study robust and meaningful. Johnson et al. (1998) found that in a study of subjects with an initial Clinical Dementia Rating (Morris et al., 1997) of 0.5, the 18 who progressed within 2 years to a Clinical Dementia Rating of 1 had significantly lower perfusion at baseline in the hippocampal–amygdaloid complex, the posterior cingulate, the anterior thalamus and the caudal portion of the anterior cingulate, compared with 27 subjects and 35 controls who did not decline.

These regions closely match those revealed by comparing our limbic and entorhinal groups. There are two apparent disparities between the studies. First, Johnson et al. (1998) described a small region of significantly reduced perfusion in the caudal portion of the anterior cingulate. In fact, this small region is revealed in our study by reducing the perfusion difference threshold to 9% in the limbic–entorhinal comparison (compare Fig. 1c with b). The second disparity is our demonstration of a reduction in perfusion in the subcallosal area.

The posterior cingulate reduction in perfusion has also been reported as an early metabolic change in Alzheimer’s disease using \(^{[18]}\text{F}\) deoxyglucose (Minoshima et al., 1997). This is a small region, only 1.7 ml at 10% perfusion change in our study, and recognition in individual studies would...
probably require registration to some form of template. As the perfusion difference threshold is reduced, this small region grows postero-superiorly up the medial banks of the parietal lobes to include the precuneus. This is a structure that shows volume loss pathologically in Alzheimer’s disease (Najlerahim et al., 1988) and activation in functional MRI studies of autobiographical memory retrieval (Maddock et al., 2001) and memory retrieval of the spatial context of lifelike events (Burgess et al., 2001). The posterior cingulate (Baleydieur et al., 1980) and, possibly the precuneus (Maddock et al., 2001), receives inputs from the parahippocampal gyrus, especially the entorhinal cortex, and also from the subiculum and presubiculum. Therefore, these regions are likely to be vulnerable to ‘disconnection’ due to pathology affecting the medial temporal lobe (Fig. 1b and c).

The subcallosal region contains a number of structures with recognized connections to memory pathways. It appears centred on Brodmann’s areas 25 and 32 of the medial prefrontal cortex, both of which receive projections from medial temporal lobe structures including the hippocampus (Barbas et al., 1999). There is a report that Alzheimer’s disease pathology has a predilection for area 25 and the posterior orbitofrontal cortex (plus anterior insula) on the basis of neurofibrillary tangles and Alz50-immunoreactive neurones (Chu et al., 1997). This was found to be less severe than in the entorhinal cortex and temporal pole, comparable with the temporal cortex and greater than in parietal, frontal or occipital cortices. Furthermore, since 99mTc-HMPAO SPET is a functional study, perfusion defects may be due to pathology in projection neurones that innervate a region (‘disconnection’), without requiring pathological changes within the affected region, as suggested by Jobst et al. (1992a). Indeed, this is likely to underlie the typical posterior temporoparietal perfusion defects seen in Alzheimer’s disease that are related to medial temporal lobe atrophy in the same hemisphere (Jobst et al., 1992a). In our study, the region of reduced perfusion extends posteriorly from the subcallosal region in a narrow band along the medial banks of the hemispheres to reach the anterior and superior aspect of the thalami. This implicates a number of very small structures including the medial and lateral septal nuclei (with well-established reciprocal connections to the hippocampus) and, more posteriorly, the anterior commissure and anterior thalamic nuclei. The nucleus accumbens (ventral striatum) is at the margin of this region, but cannot be included confidently. The mamillary bodies are probably just inferior to this region. Caution should be exercised to avoid overinterpretation of perfusion changes related to such small structures, since in the alignment of the individual SPETs there will be inevitable ‘blurring’ of the precise location of such small, centrally located structures.

Interestingly, our study demonstrates that anterior medial temporal lobe perfusion decreases by only a relatively small amount (~5%) between the limbic and neocortical stage. This may also partially explain why some previous studies in Alzheimer’s disease examining changes in perfusion over time have not remarked upon medial temporal lobe changes. Since rapidly progressive hippocampal/medial temporal lobe atrophy is well established during this ‘clinical’ phase of Alzheimer’s disease (Jobst et al., 1994; Jack et al., 1998), it suggests that perfusion changes are either discordant from atrophy in this structure or markedly precede the structural changes.

Our finding of a reduction in perfusion of a thin rind, superiorly on the anterior aspect of both cerebellar hemispheres, is novel. We are not aware of any functional imaging reports of the same result. Given that all the SPETs are fitted to standard Talairach space and that the registration of the cerebrum is generally very good, it is possible that the registration of the cerebellum is compromised in a few individuals. This could lead to artefactual perfusion ‘changes’ on the circumference of the cerebellum. Close inspection of all the registered SPETs against the Talairach template revealed only a few cases of minor inferior cerebellar ‘cut-off’, due to occasional omission of the most inferior aspect of the cerebellum from the field of view at the time of SPET acquisition. These differences cancelled across the groups. Therefore, these possible, small, anterior cerebellar perfusion changes should await confirmation from a different cohort of subjects. On the other hand, these differences between entorhinal and limbic stages may reflect an early disease process in the cerebellum associated with the atrophy and neuronal loss found there in end-stage Alzheimer’s disease (Wegiel et al. 1999).

Large bilateral posterior temporoparietal perfusion defects appear between the limbic and neocortical stages. This is thought to represent the time at which clinical symptoms first become apparent in most subjects (Grober et al., 1999). These perfusion defects are likely to remain the most important regions in aiding the differential diagnosis between Alzheimer’s disease, frontotemporal dementia and depression.

Since the duration of Alzheimer’s disease pathology and its typical temporal progression are not fully established, we attempted to clarify the temporal relationship of our observed perfusion changes. To introduce this longitudinal element to the study, templates were formed from SPET scans taken 5 years before death. Only six scans were available for each pathological stage, so these findings are less secure than those for the ‘final’ SPET groups. Taken as a whole, the results suggest a slow progression in perfusion changes through the entorhinal, and at least early limbic stages. The corollary is that this implies that the entorhinal stage is long and the limbic stage probably at least a decade, since so little change was observed over the 3-year intervals. This means that there is a significant window of opportunity for an appropriate surrogate marker to act as a diagnostic aid at this early stage in Alzheimer’s disease. The striking temporal change revealed was the development of large bilateral frontal changes in the interval from 5.06 to 2.62 years before death in the neocortical group. Furthermore, the posterior temporoparietal defects were progressive. This slow progression in
perfusion changes is in keeping with an analysis performed on a Braak-staged sample of 887 brains obtained from ‘routine autopsy’. By comparing the ages of subjects within each pathological stage, an estimate was made of the time needed for 5% of the cumulative sample to attain each stage of pathology. The results suggested at least 30 years between stage I and stage III (early entorhinal to early limbic), and ~18 years between stage III and stage V (early limbic to early neocortical) (Ohm et al., 1995).

A study based on pathological staging will be biased towards subjects with pathology, since disease-free individuals tend to live longer. We only had two subjects with no neurofibrillary pathology. However, most of our entorhinal stage subjects were regarded as OPTIMA controls, and perhaps in an ~80-year-old population the entorhinal stage is a more realistic baseline. This is in keeping with other clinico-pathological series which report neurofibrillary tangles in the transentorhinal or entorhinal cortex of almost all non-demented subjects >75 years of age (Delacourte et al., 1999). In the Braaks’ post-mortem series of 2661 unselected brains, there were 710 brains from subjects aged >81 years, of which only seven were devoid of neurofibrillary changes (Braak stage 0) (Braak and Braak, 1997). Important and very difficult to answer questions remain about the progression of entorhinal pathology. Is progression inevitable and what variation exists in the rate of progression?

The specificity of the pattern of perfusion changes with Alzheimer’s disease requires comparison with other pathologies. Vascular disease can mimic posterior temporo-parietal defects, although in clinical practice there are usually additional vascular defects present to aid diagnosis. Although there are descriptions of posterior temporo-parietal defects in Parkinson’s disease and Lewy body dementia (Lobotesis et al., 2001), these are based on clinical criteria, with all their uncertainty, and also probably do not make sufficient allowance for mixed pathologies. In Read et al. (1995), a SPET–pathological correlation in 27 patients with dementia, four subjects are described with bilateral posterior temporo-parietal defects in perfusion associated with Parkinson’s disease. However, two of these also achieved a pathological diagnosis of the so-called Lewy body variant of Alzheimer’s disease. Clinico-pathological series incorporating perfusion imaging in Lewy body dementia and Parkinson’s disease are required.

The perfusion changes associated with increasing Alzheimer’s disease pathology are clinically relevant. Posterior temporo-parietal defects are the key diagnostic aid in subjects with early dementia, in particular to differentiate Alzheimer’s disease from fronto-temporal dementia and depression. Frontal perfusion defects occur with advanced Alzheimer’s disease. These defects are easily visible on a low resolution SPET system. The earliest perfusion defects, requiring a high resolution system for confident diagnosis, are in the anterior medial temporal lobes. Recognition of perfusion decreases in these regions will be necessary to aid earlier diagnosis, particularly if disease-modifying drugs become available. This study, although using SPETs collected with a relatively low resolution system (by modern standards), exploited the power of averaging to increase ‘signal to noise’, revealing perfusion changes relevant to individual subject scans on a modern system. Therefore, retrospectively assessing individual subjects’ anterior medial temporal lobe perfusion from this study is not of value. Further work is required on high resolution systems to clarify whether unilateral anterior médial temporal lobe hypoperfusion is associated with early Alzheimer’s disease or whether bilateral hypoperfusion is required. The perfusion deficits in the subcallosal and posterior cingulate/precuneus regions found to be associated with the development of limbic stage Alzheimer’s disease pathology would require registration to normal SPET templates, and possibly occasionally also to a structural image, for robust recognition. Software to perform these tasks rapidly is widely available.

Acknowledgements

We wish to thank the volunteers in OPTIMA, the nursing team and the radiographers, and Clare Bateman for help in manuscript preparation. We thank the Medical Research Council, UK, Bristol-Myers Squibb, Amersham International and Nuclear Diagnostics for financial and technical support.

References


